European Heart Journal Supplements (2023) **25** (Supplement A), A25–A30
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suac126

ESC
European Society
of Cardiology

The impact of influenza vaccination on cardiovascular diseases

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KEYWORDS
Influenza vaccination;
Cardiovascular prevention;
Myocardial infarction;
Influenza;
Heart failure;
Cardiovascular disease

The link between influenza and medical complications is well stablished and plays a role in the high mortality rates of this disease. Available scientific evidence suggests that influenza vaccination might reduce the risk of cardiovascular events. This setting for cardiovascular prevention beyond immunoprotection has been studied in several clinical trials. Most of them include populations with coronary artery disease. However, differences in clinical design, population included, and vaccination strategies might explain divergent results and should be interpreted with caution. The present article summarizes available literature in a manner that aids physicians in a better interpretation and encourages the implementation of influenza vaccination in cardiovascular prevention programmes.

Introduction

The link between influenza and medical complications beyond the primary respiratory illness is well established and plays a role in the high mortality rates of this disease. Several population groups are at increased risk for more severe influenza illness and influenza-related mortality, including those with certain underlying medical conditions, infants, young children, and elderly adults. Analyses of risk factors for severe influenza have generally been consistent in their findings about the potential for worsening cardiovascular (CV) disease, both directly or mediated by decompensation of diabetes mellitus (DM), chronic lung disease, renal disease, or blood disorders, amongst others.

The impact of influenza vaccination on the risk reduction for CV events has been a topic of interest in several investigations. Results from observational, prospective randomized trials and meta-analyses have progressively added mounting evidence for the cardioprotective effects of vaccination. However, results are not consistent in all of the studies. Differences in trial design, sample size, patients with/without CV disease (CVD), acute/chronic settings, type of vaccine administered, follow-up, endpoints considered, and other characteristics might play a role in this heterogeneity.

The following aims to summarize the evidence for influenza vaccination as a strategy to reduce the risk of CV events.

Viral illness and cardiovascular health

We have learned how influenza infection triggers mechanisms that potentially affect CV health, especially in individuals considered at high morbidity and mortality risk based on their CV risk factors or the presence of etablished CVD.[1,2] Appropriate risk factor control and optimal medical therapy for their baseline conditions are the first step to prevent influenza-mediated complications in these patients. Yearly influenza vaccination is also strongly encouraged in this population based on the favourable balance between benefits and risks. It has been a field of continuous research in large clinical trials in order to provide effective immunoprotection and favourable safety profiles. The main settings where influenza vaccination has been studied are coronary artery disease (CAD) and heart failure (HF).

Influenza vaccination and coronary artery disease

Naghavi *et al.*[3] reported in 2000 that influenza vaccination in patients with chronic CAD was negatively associated

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with the development of new myocardial infarction (MI) during the winter influenza season (October 1997 to March 1998). Although this was a retrospective, case-control study and vaccination status was self-reported, it constitutes one of the first reports of the potential association of influenza vaccination with reduced risk of subsequent MI. Because of its nature, the study was not able to determine the mechanisms that lead to lower the risk of MI in vaccinated individuals [0.33; 95%, confidence interval (CI) 0.13–0.82; $P = 0.017$].

Similarly, Lavallee *et al.*[4] found that the CAD patients vaccinated during the epidemiological campaign had lower rates of cerebrovascular accidents in the winter of 1999–2000 in Paris, France.

The first randomized study trying to revalidate Naghavi *et al.*'s results included 301 patients with MI and planned percutaneous coronary intervention (PCI).[5] The 'Flu vaccination in Acute Coronary Syndromes and Planned Percutaneous Coronary Interventions (FLUVACS)' trial evaluated the effects of influenza vaccination by comparing the incidence of CV death at 6 months in patients who received vaccination with a control group (no vaccination). This primary outcome at 6 months occurred in 2% of the patients in the vaccination group vs. 8% in controls (relative risk [RR] 0.25; 95% CI 0.07–0.86; $P = 0.01$). The secondary triple composite endpoint rates (CV death, non-fatal MI, or recurrent angina prompting re-hospitalization) occurred in 11% of the patients in the vaccination group vs. 23% in controls (RR 0.50; 95% CI 0.29–0.85; $P = 0.009$).[5]

The benefit of vaccination was limited to patients with MI, and no differences appeared for planned PCI patients.[6] Vaccination reached a greater reduction in the incidence of the composite endpoint among subgroups with a higher baseline risk (age >65, diabetic patients, TIMI risk score ≥6). However, the benefits of vaccination were also seen in those who a priori were not at high risk (non-diabetic patients, non-smokers, and patients with no history of revascularization). The authors conducted follow-up studies in order to determine whether the observed benefits of vaccination were maintained over time. The same endpoint definitions were used for 1-year and 2-year follow-up analysis[7] among those who were re-vaccinated during the subsequent winter season.[8] They found that the incidences of CV death [(6 vs. 17%; $P = 0.002$) (HR [hazard ratio] = 0.34; 95% CI: 0.17–0.71; $P = 0.02$)], the composite endpoint of total death/MI [(3.5 vs. 9.7%; $P = 0.005$) (HR = 0.36; 95% CI: 0.12–1.09; $P = 0.05$)], and the triple composite endpoint of CV death, non-fatal MI, or recurrent angina [(22 vs. 37%) (HR = 0.59, 95% CI: 0.4–0.86; $P = 0.004$)] at 1 year were significantly lower in patients receiving vaccination compared with controls.[7,8]

These results suggested that influenza vaccination improved the clinical course of CAD in patients with MI and that the beneficial effect would extend over the period of viral circulation.

The 'Influenza Vaccination In Secondary Prevention From Coronary Ischaemic Events In Coronary Artery Disease—FLUCAD trial' was designed as a prospective, randomized, double-blind, placebo-controlled study that tried to evaluate the effect of influenza vaccination (trivalent influenza vaccination vs. placebo) on the incidence of coronary ischaemic events in optimally treated patients with CAD confirmed by coronary angiography.[9] The risk of the population included (658 outpatients with optimally treated) was lower than the FLUVACS trial.[5] There was no statistical difference in CV death (1.06; 95% CI, 0.15–7.56; $P = 0.95$) or the combined endpoints (including CV death, MI, coronary revascularization, or hospitalization for myocardial ischaemia) (Table 1), though the point estimate for the latter favoured vaccination. This should not be regarded as a negative result, since influenza vaccination might improve the clinical course of CAD by reducing the frequency of coronary ischaemic events at 12 months (6.02 vs. 9.97%, HR 0.54; 95% CI: 0.29–0.99; $P = 0.047$).[9]

Patients with previous MI or stable angina were randomized to receive influenza vaccination as an adjunctive secondary prevention strategy or placebo in the influenza vaccination in reducing cardiovascular events in patients with coronary artery diseases (IVCAD) trial with a single-blind design. Results were only published as abstract,[10] with no significant reduction in the primary endpoint (CV death) but less influenza infection rate ($P = 0.0049$) in the vaccination group. However, the number of total events for the primary endpoint was too low (1 vs. 2) to raise enough statistical power[10] (Table 1).

The positive effect of influenza vaccination after admission for the acute coronary syndrome (ACS) was further confirmed in another randomized clinical trial (RCT). The fact that vaccination benefits persist even with the advances in the acute and log-term treatment options (primary PCI, antithrombotic treatments, newer stent generations, lipid-lowering drugs, etc.) gives consistency to the findings of subsequent investigations.

In 2011, Phrommintikul *et al.*[11] published their results comparing a vaccination strategy vs. control on 439 patients admitted for ACS in the previous 2 weeks. The composite endpoint including CV death, ACS hospitalization, HF hospitalization, and stroke hospitalization was reduced by 30% in the vaccination group. Cardiovascular death was explored as a secondary endpoint and showed reduced incidence (by 27%) in those who received the vaccine.

The Influenza Vaccination After Myocardial Infarction (IAMI) trial is probably the trial with the strongest impact on the field of CAD and influenza vaccination.[13] Participants were enrolled within 72 h of an invasive coronary procedure or hospitalization and then randomized (1:1) to receive trivalent influenza vaccine or placebo.[14] This included not only ST-elevation MI (STEMI) and non-STEMI (NSTEMI) diagnosis but also patients with stable CAD ≥75 years undergoing angiography/PCI and with ≥1 additional risk criterion (previous MI, previous PCI, previous coronary artery bypass graft CABG, DM, current smoking, or an estimated glomerular filtration rate (eGFR) <40 mL/min).

The sample size was initially calculated on the basis of three smaller randomized studies,[7,9,11] demographic data from the Annual Swedish Coronary Angiography and Angioplasty Registry reports (accessible at https://www.ucr.uu.se/swedeheart/) and from the Thrombus aspiration during ST-segment elevation myocardial infarction (TASTE) trial in which the number of risk patients included was lower than expected.[15] The combined primary endpoint of all-cause death, MI, or stent thrombosis at 12 months was estimated at 10% (expected survival probability of 0.9) for individuals randomized to placebo. With a 5% two-sided significance level, the authors calculated that 386 events would be needed to have a 80% statistical power to detect a 25% reduction of the primary endpoint in the influenza vaccination group (corresponding to a

Table 1 Clinical trials of influenza vaccination and cardiovascular disease

References	Design	n/duration	Baseline population	Therapy	Endpoints	Results (HR, RR, or OR)
Gurfinkel *et al.*[5] (FLUVACS)	RCT	301/6 m	Inpatients with ACS or outpatients with stable CAD and planned PCI	Influenza vaccination vs. placebo	1° CV death at 6 m 2° CV death/MI/re-hospitalization for severe recurrent ischaemia	0.25; 95% CI, 0.07-0.86 ($P=0.01$) 0.50; 95% CI 0.29-0.85 ($P=0.009$)
Gurfinkel *et al.*[7] (FLUVACS)	RCT	301/12 m	Inpatients with ACS or outpatients with stable CAD and planned PCI	Influenza vaccination vs. placebo	1° CV death at 1 year 2° CV death/MI/re-hospitalization for severe recurrent ischaemia	0.34; 95% CI, 0.17-0.71 ($P=0.002$) 0.59; 95% CI 0.4-0.86 ($P=0.004$)
Ciszewski *et al.*[9] (FLUCAD)	RCT	658/12 m	Outpatients with CAD optimally treated	Influenza vaccination vs. placebo	1° CV death 2° CV death/MI/coronary revascularization 2° CV death/MI/coronary revascularization/hospitalization for myocardial ischaemia	1.06; 95% CI, 0.15-7.56 ($P=0.95$) 0.54; 95% CI, 0.24-1.21 ($P=0.13$) 0.54; 95% CI, 0.29-0.99 ($P=0.047$)
Keshtkar-Jahromi *et al.*[10] (IVCAD)	RCT randomized, single-blind, placebo-controlled	281/6 m	Patients with CAD	Influenza vaccination vs. placebo	1° CV death 2° ACS (MI or unstable angina) 2° Admission for CAD 2° Angina severity 2° Coronary artery stenosis 2° Coronary revascularization (CABG or PCI) 2° Influenza infection	Abstract published reports: - 1 vs. 2 death in treatment vs. control group. - Less influenza infection ($P=0.0049$) - No other 2° endpoint significant differences
FLUVACS-IC	RCT	117/6 m	Severe acute HF patients (requiring ventilator supportand aggressive medical therapy).	Influenza vaccination vs. control	1° Overall mortality 2° Re-hospitalization for any cause or infarction	0.16; 95% CI, 0.33-0.7 ($P=0.022$)
Phrommintikul *et al.*[11]	RCT	439/12 m	Patients with ACS in the previous 8 weeks	Influenza vaccination vs. control	1° CV death, ACS hospitalization, HF hospitalization, stroke hospitalization. 2° CV death	0.70; 95% CI, 0.57-0.86 ($P=0.004$) 0.73; 95% CI, 0.55-0.91 ($P=0.032$)
Lavallée *et al.*[12]	Pooled data from 3 trials	23 110/2 years	Patients with recent TIA or stroke	Influenza vaccination status (yes vs. no)	1° Non-fatal MI, non-fatal stroke, or vascular 2° MI 2° Stroke	0.97; 95% CI, 0.85-1.11 ($P=0.67$) 0.84; 95% CI, 0.59-1.18 ($P=0.30$) 1.01; 95% CI, 0.88-1.17 ($P=0.89$)
Frobnert IAMI	RCT single-blind, placebo-controlled	2,532/12 m	Patients within 72 h of PCI for STEMI/NSTEMI[a]	Influenza vaccination vs. placebo	1° All-cause death, MI, stent thrombosis 2° All-cause death 2° CV death 2° MI 2° Stent thrombosis	0.72; 95% CI, 0.52-0.99 ($P=0.04$) 0.59; 95% CI, 0.39-0.89 ($P=0.010$) 0.59; 95% CI, 0.39-0.90 ($P=0.014$) 0.86; 95% CI, 0.50-1.46 ($P=0.57$) 1.94; 95% CI, 0.48-7.76 ($P=0.34$)
Vardeny INVESTED	RCT double-blind	5,260/3 years	Patients with recent MI or hospitalization for HF plus an additional factor[b]	High-dose TIV vs. standard-dose QIV	1° All-cause death/CP hospitalization (1 year) 2° Total CP hospitalizations or death (3 years) 2° CV death or hospitalization (1 year) 2° Death or CP hospitalization (3 years) 2° First CP hospitalization/all-cause death (3 years)	1.06; 95% CI, 0.97-1.17; ($P=0.21$) 1.08; 95% CI, 0.97-1.20; ($P=0.16$) 1.01; 95% CI, 0.84-1.21; ($P=0.96$) 1.04; 95% CI, 0.94-1.15; ($P=0.44$) 1.05; 95% CI, 0.96-1.15; ($P=0.26$)
Loeb IVVE	RCT quadruple-blind	5,129/36 m	Heart failure patients ≥18 years and NYHA functional class II-IV	Inactivated TIV influenza vaccination vs. placebo administered annually for 3 influenza seasons	1° Composite adverse CV event: CV death/non-fatal MI/non-fatal stroke/HF hospitalization 2° CV death at 6 m	0.93; 95% CI, 0.81-1.07 ($P=0.30$) 0.89; 95% CI, 0.77-1.04 ($P=0.13$)
Fonseca VIPS-ACS	RCT open-label, active-controlled, blinded outcome adjudication	1,801/12 m	Patients within 7 days of hospital admission for STEMI/NSEMI not previously vaccinated for the current influenza season	QIV double dose during the ACS hospitalization vs. QIV standard dose 30±5 days after randomization	1° Composite of death/MI, stroke, unstable angina hospitalization, HF hospitalization, urgent coronary revascularization, or respiratory infection hospitalizations. 2° CV death, MI, or stroke. 2° Overall mortality 2° CV death 2° MI 2° Unstable angina hospitalization 2° Stroke 2° HF hospitalizations 2° Hospitalization for urgent coronary revascularization 2° Stent thrombosis	1.00; 95% CI, 078-1.28 ($P=0.99$) 0.94; 95% CI, 0.66-1.33 ($P=0.72$) 1.08; 95% CI, 0.77-1.51 ($P=0.67$) 1.25; 95% CI, 0.77-2.03 ($P=0.36$) 0.88; 95% CI, 0.49-1.59 ($P=0.68$) 1.86; 95% CI, 0.69 - 5.03 ($P=0.22$) 1.11; 95% CI, 0.62-2.01 ($P=0.72$) 0.88; 95% CI, 0.49-1.59 ($P=0.68$) 0.91; 95% CI, 0.37-2.24 ($P=0.68$) 1.01; 95% CI, 0.25-4.05 ($P=0.98$)
Hollingsworth NCT04137887	Pragmatic registry-based RCT Modified double-blind	>120 000/over 3 influenza seasons	Healthy volunteers ≥65 years	QIV-SD vs. QIV-HD	1° effectiveness for the prevention of CV and/or respiratory hospitalizations 2° clinical relative effectiveness of QIV-HD as compared to QIV-SD in the prevention of: - inpatient hospitalization for selected circulatory and respiratory causes - death, either all-cause or CV or respiratory causes - inpatient hospitalization (using primary and secondary discharge diagnoses) - inpatient hospitalization (using admission diagnoses) - hospital emergency room visits - primary care visits to the physician or - MACE - To assess the characteristics of inpatient hospitalization or hospital emergency room visits or primary care visits to the physician by QIV-HD and QIV-SD groups - To describe the clinical relative effectiveness of QIV-HD as compared to QIV-SD by age group/by group with specific comorbidities/for different	Ongoing

Continued

Table 1 Continued

References	Design	*n*/duration	Baseline population	Therapy	Endpoints	Results (HR, RR, or OR)
Johansen DANFLU 1	Pragmatic registry-based RCT parallel open-label	12 477/influenza season 2021-2022	Danish citizens aged 65-79 years	QIV-HD vs. QIV-SD	periods of observation - To describe all SAEs 1° Feasibility of conducting a pragmatic randomized clinical trial in Denmark comparing QIV-HD to QIV-SD in the 2021/2022 influenza season in a registry-based setting. 2° Relative vaccine effectiveness of the QIV-HD compared to QIV-SD for a range of CV and respiratory endpoints. a) hospitalization for influenza or pneumonia b) all-cause mortality c) hospitalization for CV disease d) hospitalization for cardiorespiratory disease e) hospitalization for respiratory disease f) hospitalization for any cause g) hospitalization for COVID-19	1° Complete follow-up for 99.97% of patients 2° Significant vaccine effectiveness of QIV-HD vs. QIV-SD was found for the following endpoints: a) 64.4%; 95% CI, 24.4%-84.6% b) 48.9%; 95% CI, 11.5%-71.3%

ACS, acute coronary syndrome; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CV, cardiovascular; MI, myocardial infarction; TIA, transient ischaemic attack; HF, heart failure; CABG, coronary artery bypass graft; CP, cardiopulmonary; HR, hazard ratio; INVESTED, INfluenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure; IVCAD, influenza vaccination in reducing cardiovascular events in patients with coronary artery diseases; IVVE, Influenza Vaccine to Prevent Adverse Vascular Events; MACE, major acute cardiovascular events; RR, relative risk; SAEs, serious adverse events; STEMI, ST-elevation-myocardial infarction; NSTEMI, non-STEMI; NYHA, New York Heart Association; TIV, trivalent influenza vaccine; QIV, quadrivalent influenza vaccine; QIV-SD, quadrivalent influenza vaccine standard dose; QIV-HD, quadrivalent influenza vaccine high dose.

[a]The Influenza Vaccination After Myocardial Infarction (IAMI) trial also included patients with stable CAD ≥75 years undergoing angiography/PCI and with ≥1 additional risk criterion (previous MI, previous PCI, previous CABG, DM, current smoking, or an estimated glomerular filtration rate (eGFR) <40 mL/min).

[b]Additional risk factors: prior MI (if HF the index event above or a second MI), prior HF hospitalization (if MI the index event above or a second HF event); age ≥ 65; left ventricular ejection fraction <40%; diabetes mellitus; obesity (Body Mass Index ≥ 30); renal impairment (eGFR ≤ 60); history of ischaemic stroke; history of peripheral artery disease; current smoking.

HR of 0.75). That meant a number of 2186 individuals per treatment arm. In order to control for dropouts and cross from one group to the other, the proposed enrolment sample size was 4400 patients. However, the inclusion stopped early due to the COVID-19 pandemic with only 58% of target enrolment (2532 patients).

The primary endpoint (composite of all-cause death, MI, or stent thrombosis at 12 months) was reduced by 28% in the vaccination group compared with placebo (5.3 vs. 7.2%, HR 0.72; 95% CI: 0.52-0.99; $P = 0.040$).[13] These results were consistent by subgroups defined by sex, age (<65 vs. ≥65 years), DM status, smoking status, previous MI, STEMI vs. NSTEMI, and influenza season. Key secondary outcomes showed a 41% reduction in CV mortality and a 41% reduction in all-cause mortality. The findings for MI trended in a favourable direction but were not statistically significant, which may have been attributable to low numbers of events and limited statistical power. The authors also combined the IAMI results in a meta-analysis with three other trials and demonstrated a 49% reduction in CV death [pooled HR, 0.51 (95% CI, 0.36-0.71)].[13] Limitations include the early termination of the trial, which might have exaggerated the estimates of the benefits of vaccination. In addition, the generalizability of the results to the subgroup of women should be made with caution, since they were underrepresented (women comprised only 19% of participants).

The observed 41% reduction in both all-cause and CV death might place this trial in a remarkable position, especially in the actual context of effective secondary prevention pharmacological interventions. β-blockers, statins, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers reduce the risk of reinfarction in the range of 20-25% post-MI.[16] Relative risk reductions for different pharmacotherapies cannot be directly compared across studies given different study designs and background risk of study populations. However, patients in the IAMI trial were very well treated with contemporary medical therapy at discharge post-MI, with 98% on aspirin, 97% on P2Y12 inhibitor, 70% on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, 78% on β-blockers, and 98% on statins. Although the benefit of the influenza vaccine was incremental to that, it has not been given the same level of attention or priority as a secondary prevention strategy. The authors suggest that all patients post-MI should be offered vaccination in the hospital before discharge if not already vaccinated that season. Because acute CV events have also been demonstrated with COVID-19 infection, COVID-19 vaccination is also strongly recommended for patients with or at risk for CVD.[17]

Influenza vaccination research after the IAMI trial

Upcoming research on influenza vaccination for CAD patients might determine whereas trivalent vs. quadrivalent, standard vs. high-dose vaccination, inpatient vs. ambulatory settings, further and safely improve outcomes. Trial designs and result interpretation must take into account that, more than superiority, these trials would try to reassure the proven benefits of influenza vaccination in CAD patients and how the introduction of

newer vaccines and vaccination strategies impact those results. For instance, results from the Vaccination against Influenza to Prevent cardiovascular events after Acute Coronary Syndromes (VIP-ACSs) study were released at the European Society of Cardiology (ESC) Congress 2022 (Barcelona)[18] and recently published.[19] The authors found no differences on cardiopulmonary outcomes (Table 1) when comparing a double-dose quadrivalent influenza vaccine before hospital with outpatient standard-dose vaccination among patients hospitalized for ACS. These results should not be regarded as negative. In fact, the trial demonstrated that adverse events were infrequent and did not differ between double or standard doses. The non-inferiority of the strategies adds another piece of evidence for considering influenza vaccination before hospitalization discharge, not only as an immunoprevention strategy avoidance of viral illness but also as a secondary prevention tool for the avoidance of CV morbidity and mortality.

Similar interpretations are needed for the results of vaccination trials conducted on HF patients (Table 1), such as INfluenza Vaccine to Effectively Stop Cardio Thoracic Events and Decompensated Heart Failure (INVESTED)[20,21] and Influenza Vaccine to Prevent Adverse Vascular Events (IVVE)[22,23] (results presented as an abstract) (Table 1). Finally, recent designs are focusing on the feasibility of randomizing different populations (by age, underlying disease), such as recently presented (ESC Congress, Barcelona 2022) DANFLU-1 trial[24] (Table 1) or ongoing trial in people aged over 65 years.[25]

The clinical research gap

The suboptimal uptake of influenza vaccine among patients with CVD could improve if cardiologists took greater awareness and ensured their patients annually received this important, guideline-recommended CV preventive measure. As part of a team-based approach to care, this should also fall within the scope of switching the setting where the vaccine is administered. Instead of relegated to primary care scenarios, hospital admission, rehabilitation programmes, ambulatory visits, or even other secondary prevention practices (inhibitors of proprotein convertase subtilisin/kexin type 9 serine protease [iPCSK9], inclisiran injections) might constitute excellent opportunities to provide influenza vaccines to high-risk patients with CVD.

Funding

This paper was published as part of a supplement financially supported by Sanofi. Manuscripts were accepted after rigorous peer review process that was managed by an expert Guest Editor independently appointed by the Editor-in-Chief. The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of Sanofi.

Conflict of interest: None declared.

Data availability

No new data were generated or analysed in support of this research.

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